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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/002,698	12/05/2001	Snezna Rogelj	UNME-0115-1	4017

7590 07/02/2004

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/002,698	ROGELJ ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-15 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15 and 19-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

In the response filed 5/24/04, applicants requested a change in their election from Group 3 to group 1. This request is granted, and moreover, claims 12-15, 19 and 21 are rejoined therewith. Claims 9-15 and 19-21 remain pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-15 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification asserts (e.g., page 1, lines 12-14) that the claimed compounds are effective to inhibit PDI, and to induce shedding of L-selectin from leukocytes. On page 4, it is asserted that figure 4 provides evidence that the compound designated PAODMPS* is effective to induce L-selectin shedding from unspecified cells. The compound PAODMPS* is the product of reaction between 2, 3-dimercapto propanesulfonic acid and phenylarsine oxide, the structure of which is provided on page 25 of the specification. In addition, figure 3 shows that when the compound designated PAO* [*para*-N-(ethane-2-

sulfonic acid)amino phenylarsenoxide] was contacted with neutrophils, the result was that less L-selectin could be detected in an unspecified assay. The fact that less L-selectin could be detected in an unspecified assay could be interpreted to mean either that PAO* is effective to promote L-selectin shedding or that PAO* is effective to inhibit L-selectin shedding. It is expected that applicants will assert that the result of figure 3 should be interpreted to mean that *para*-N-(ethane-2-sulfonic acid)amino phenylarsenoxide is effective to promote L-selectin shedding from neutrophils. The point is, however, that regardless of what results may have been obtained for the compound designated PAODMPS*, or for *para*-N-(ethane-2-sulfonic acid)amino phenylarsenoxide, neither of these two compounds falls within the scope of the claimed invention. The claims are drawn to substituted oxazole arsenoxides. The fact that there may exist other compounds, falling outside the scope of the claimed invention, that exhibit a particular activity does not mean that the claimed compounds will promote L-selectin shedding, or that the claimed compounds will inhibit PDI. The skilled artisan cannot "predict" which compounds will promote L-selectin shedding merely by viewing its structure. Consider, for example, the following references:

- Bennett T. A. (*Journal of Immunology (Baltimore, Md. : 1950)* **156** (9) 3093-7, 1996) discloses that the compound ((N-(D,L- [2- (hydroxyaminocarbonyl)-methyl]- 4- methylpentanoyl)- L- 3- (tert- butyl)- alanyl-l -alanine, 2-aminoethyl amide) fails to promote L-selectin shedding.

- Borland, G. (*Journal of Biological Chemistry* **274** (5) 2810-5, 1999) discloses that compounds designated Ro 31-9790 and KD-IX-73-4 fail to promote L-selectin shedding, and that TIMP-3 also fails to promote L-selectin shedding. [The compounds designated Ro 31-9790 and KD-IX-73-4 are hydroxamic acid-based inhibitors of metalloproteinases]

- Solito, Egle (*FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **17** (11) 1544-6, 2003) discloses (e.g., page 1544, col 2) that the receptor antagonist Boc1 fails to promote L-selectin shedding, and that the calcium entry blocker SKF-96365 similarly fails in this regard.

- Asimakopoulos G. (*Perfusion* **15** (6) 495-9, 2000) discloses that aprotinin fails to promote L-selectin shedding,

- Spoelstra F. M. (*American journal of respiratory and critical care medicine*, **162** (4 Pt 1) 1229-34, 2000) discloses that the compounds budesonide and formoterol both fail to promote L-selectin shedding.

- Recchioni R. (*Biochemical and biophysical research communications* **252** (1) 20-24, 1998) discloses that melatonin fails to promote L-selectin shedding.

- Hafezi-Moghadam A (*Journal of Experimental Medicine* **193** (7) 863-72, 2001) discloses that the compounds dexamethasone and morphine both fail to promote L-selectin shedding.

- Davenpeck K. L. (*Journal of immunology* (Baltimore, Md. : 1950), **165** (5) 2764-72, 2000) discloses (e.g., figure 4) that each of the following compounds failed to promote L-selectin shedding: EDTA, phenanthroline, batimastat, and marimastat

- Alexander S. R. (*Journal of Leukocyte Biology* **67** (3) 415-22, 2000) discloses that the protein kinase C inhibitor staurosporine failed to promote L-selectin shedding.

Thus, one cannot predict, merely by viewing a structure, which compounds will inhibit L-selectin shedding, which compounds will promote L-selectin shedding, and which will do

neither.

But suppose, at some point in the future, that applicants were able to show that the claimed compounds are effective to promote L-selectin shedding. The next question will be, can the skilled artisan "predict" that PDI will be inhibited? In reality, the "state of the art" in May of 1997 was such that there was no reason to expect any correlation between the propensity of a compound to promote L-selectin shedding, and its propensity to inhibit PDI. And if, at some point in the future, applicants were able to show that the claimed compounds are effective inhibitors of PDI, the next question is whether that translates into an inhibition of viral replication, even *in vitro*. It is noted that Ryser (*Proc Natl Acad Sci* **91**, 4559, 1994) has speculated that PDI may be necessary for virus cell fusion and HIV entry. However, this was not demonstrated conclusively. It may be the case that other investigators have shown, subsequent to May 1997 that PDI **is** necessary for virus /cell fusion and HIV entry. However, the state of the art at the time of the invention did not support the notion that if a compound inhibits PDI, a skilled artisan can reliably "predict" inhibition of virus /cell fusion. And even if applicants could show that the claimed compounds can inhibit viral entry into certain types of cells, it will not follow therefrom that HIV infections in humans can be successfully treated. The fact is that *in vitro* inhibition of HIV replication is not predictive of an effective therapy in humans. As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of

need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As stated in Mangos (*Texas Medicine*, **86**, 40, 1990):

> "In spite of ... [therapy against HIV and opportunistic infections], the universal outcome of HIV infection / AIDS is the death of the patients" (see, e.g., abstract).

As disclosed in Binquet (*AIDS* **12**, 2313, 1998) a total of 556 patients were treated with HIV protease inhibitors for a period of 230 days, and that despite being treated with with HIV protease inhibitors for more than seven months, 24 of the patients had died. Both of these references teach that death occurs in spite of administration of HIV protease inhibitors. If death is the result of a treatment, one cannot say that success (in the treatment) is predictable.

If sucess is not predictable, it must be "unpredictable". Given that treatment of AIDS is "unpredictable", it follows therefrom that "undue experimentation" would be required to determine which, if any, of the claimed compounds can be used to treat patients afflicted with AIDS. [*Ex parte Balzarini,* 21 USPQ2d 1892)]. Thus, extrapolation from *in vitro* inhibition of viral replication in a petri dish to a therapy in humans is unpredictable.

Thus, (a) it remains to be determined whether there exists a biological assay such that the claimed compounds will exhibit a positive (or negative) result; (b) it remains to be determined whether the claimed compounds can promote L-selectin shedding from

neutrophils, or any other cells, for that matter; (c) even if it turns out that the claimed compounds can promote L-selectin shedding from neutrophils, the reality is that one cannot "predict" whether such compounds will inhibit PDI; (d) even if it turns out that the claimed compounds will inhibit PDI, this will not mean that the skilled artisan can reliably "predict" whether the compounds will inhibit entry of HIV into cells; (e) even if it could be shown that the claimed compounds inhibit entry of HIV into cells, it will not follow therefrom that treatment of HIV infections in humans can be successfully treated.

Accordingly, "undue experimentation" will be required to practice the claimed invention.

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Claims 9-15 and 19-21 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 9 recites that "at least one of R and R' is a charged ligand". Claim 9 would permit both of R and R' to be a charged ligand, but the claim would also permit just one of R and R' to be a charged ligand. For the case of just one of R and R' representing a charged ligand, the claim is indefinite as to what the other substituent variable can be.

- Claim 12 is drawn to a method for inhibiting PDI compounds exposing". Perhaps the word "compounds" should instead be *comprising*.

- In claim 12, the term "PDI" may be used if accompanied by an explanation of what this abbreviation represents.

- Claim 13 recites "the method of claim 12 wherein PDI activity is 35". Here, the number "35" may be superfluous.

- In claim 19, process steps are missing. Suppose that in a healthy person, the level of L-selectin shedding is determined to be "X", and that in an HIV-infected person, the level of L-selectin shedding is is determined to be "Y". What would the skilled artisan do at that point? Would the fact that one person exhibits "X" level, and another person exhibits "Y" level mean that an optimal blood concentration (of a PDI inhibitor) has been achieved, or are there other process steps that must be undertaken?

✺

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.